CARBIMAZOLE (NEO-MERCAZOLE) IN THYROTOXICOSIS—A REVIEW OF SIXTY PATIENTS

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CARBIMAZOLE (2 Carbethoxy-thio-1-methyl glyoxaline) was first introduced by Lawson, Rimington, and Searle (1951). Early reports by Lawson and Barry (1951), Macgregor and Miller (1953), Doniach (1953) and Poate (1953) stressed the freedom from toxicity and potency of carbimazole as an anti-thyroid drug. Though potent, thiourea derivatives had proved to have a significant toxic risk. For this reason, most recent workers have concentrated on a comparison of carbimazole with thiourea drugs in regard to studies of toxicity. McGavack, *et al.* (1956), in describing their experiences in forty-one cases with special reference to speed of control of symptoms, remark on the sparsity of reports of clinical experience with carbimazole.

The purpose of the present paper is to record observations made in a group of thyrotoxic patients concerning short- and long-term effects and drug toxicity. An assessment of the place of carbimazole in treatment and factors which may influence the response of thyrotoxic patients to the compound are recorded.

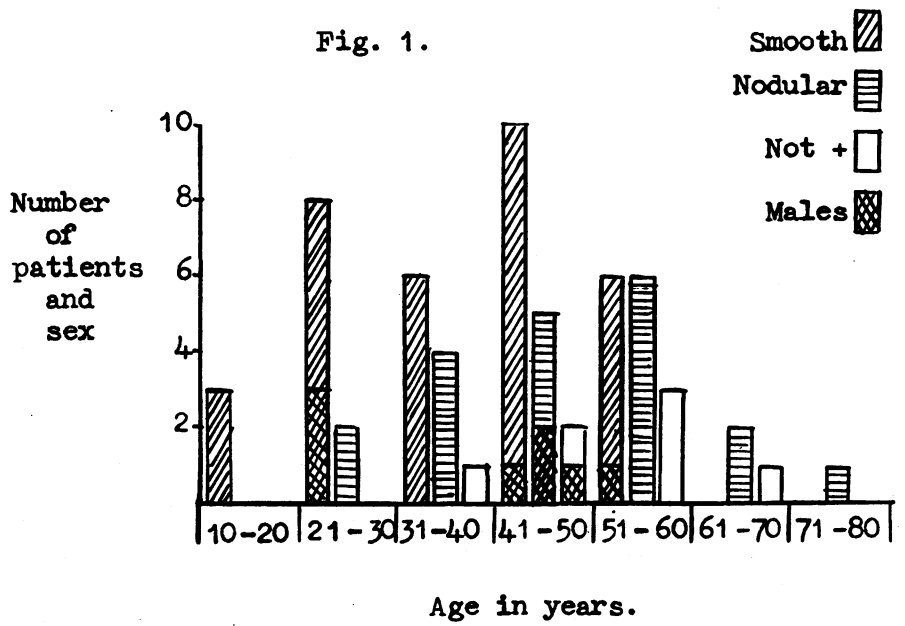

Fig. 1—Distribution according to sex and age in 60 thyrotoxic patients.

Methods and Plan of Study.

Sixty non-selected patients were studied, comprising 52 female and 8 male patients, of age ranging from 17-74 years. The distribution according to age, sex, and gland type is shown in Fig. 1. Symptoms were present for from 12 days to 3 years (average 11 months) at the time of first attendance. The average duration of symptoms before attendance for smooth toxic goitre was 7 months and for nodular goitre 10 months. Sixty-six per cent. of patients attended within 6 months and 82 per cent. within a year.

Fig. 2.

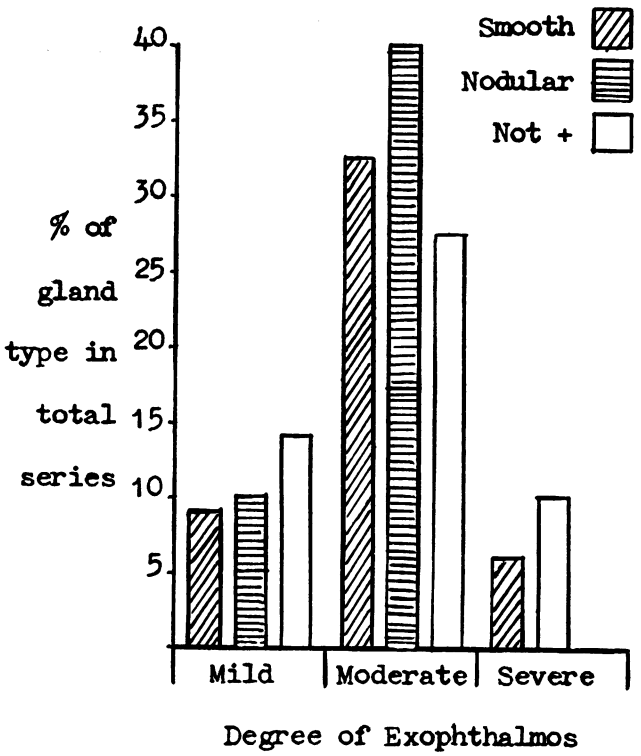

Fig. 2—Incidence of degrees of exophthalmos as a percentage of gland type.

The type and degree of thyroid enlargement were assessed clinically on each visit. A smooth goitre was noted in 33 patients, nodular gland in 20, and in 7 patients no clinical enlargement was demonstrable (Not +).

Eye changes were judged clinically in 3 grades, the least marked being a thyrotoxic stare with lid lag and the most severe indicating marked exophthalmos with or without ophthalmoplegia. Moderate grades fell between these two

extremes. The incidence of eye changes related to the gland type is shown in Fig. 2. There were eye signs in 50 per cent. of the 60 patients.

The diagnosis of thyrotoxicosis was made clinically with confirmation in 34 patients by I_{131} uptake and by basal metabolic rate estimation in 3 cases. Serum cholesterol was assessed at the first attendance in 15 patients. In 3 the result was 200 mg./100 ml. or more and in the remainder averaged 167 mg./100 ml.

All patients were started on carbimazole 30 mgs. to 45 mgs. daily in three doses. L-thyroxine-sodium 0.1-0.3 mg. was given concurrently with the dosage of carbimazole to reduce the risk of goitrogenesis (Astwood, *et el.*, 1943; Purves, 1943; Fraser, *et al.*, 1954) and to avoid aggravation of eye signs (Fraser and Wilkinson, 1953).

Throughout the investigation, the patients were examined at intervals of 1-3 months, the attendances being at approximately the same time on each occasion in relation to meal times. As far as possible, each was weighed in the same attire on each attendance. Routine differential and total white cell counts were undertaken on each visit. The decision as to when each patient was euthyroid was assessed clinically.

All patients treated medically had at least 12 months' treatment and varied on average between 14-16 months. Carbimazole was gradually withdrawn, the dose in most patients being reduced to 5 mgs. daily, followed by 5 mgs. on alternate days, without added thyroxine in the last few months of treatment. Supervision has been continued up to 30 months after stopping carbimazole.

Fig. 3.

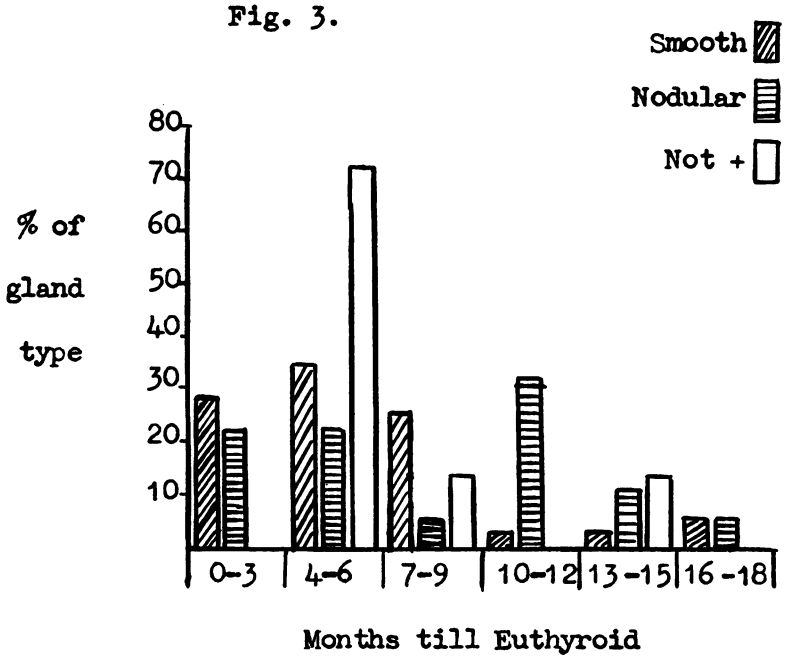

Fig. 3—Time required in gland types for establishment of a euthyroid state.

Results.

1. The Anti-Thyroid Effect.

Most patients on carbimazole 15 mgs. three times daily with l-thyroxine sodium 0.1 mg. twice daily reported an improvement in symptoms in 2-4 weeks. The establishment of a clinically assessed euthyroid state took much longer. For smooth goitres, 2-17 months (average 6 months) was required, for nodular goitre 3-17 months (average 8 months), and where the gland was not palpable 4-14 months (average 7 months) was necessary. Resistant cases are excluded from the above assessments.

Sixty-two per cent. of the patients with smooth goitres were euthyroid in 6 months as compared with 43 per cent. with nodular glands. Fig. 3 shows the time taken for a euthyroid state in relation to the gland type and the outcome of carbimazole treatment in the total series is shown in Table 1.

TABLE 1.

Analysis of Carbimazole Treatment in 60 Thyrotoxic Patients.

Outcome of Carbimazole Treatment	Gland Type				% of Total
	Smooth	Nodular	Not +	Total	
Elective Surgery	6	3	–	9	15
Elective I_{131}	2	1	–	3	5
Toxic Response	2	–	–	2	3
Resistance to the drug	–	2	–	2	3
Still on treatment	2	2	–	4	7
Definitive Carbimazole—					
Remissions	16	4	5	25	42
Relapses	5	8	2	15	25
Total	33	20	7	60	100

Of the 60 patients, carbimazole was used as a preliminary to an elective operation in 9 cases (15 per cent.)—6 smooth and 3 nodular—and as a preparatory treatment to radioactive iodine in 3 cases (5 per cent.)—2 smooth and 1 nodular. One patient was treated by sub-total thyroidectomy on account of granulopenia while another required treatment with radioactive iodine for agranulocytic angina. Of the remaining 46 cases, 2 showed resistance to the drug. One of these has received 45 months' treatment and is still toxic, requiring high dosage, while the other has had 39 months' adequate treatment with incomplete control. Four patients are still on treatment, 19 months, 22 months, 23 months, and 34 months at the time of reporting. They are reasonably well controlled while on the drug.

The remaining 40 patients (67 per cent.) proved amenable to treatment with carbimazole. Twenty-five (62.5 per cent.) of these have had remissions following cessation of treatment for from 5-30 months (Table 2). Fifteen cases (37.5 per cent.) have relapsed. The time following treatment at which relapse occurred

TABLE 2.

ANALYSIS OF REMISSIONS AND RELAPSES IN 40 PATIENTS FOLLOWING CARBIMAZOLE THERAPY.

MONTHS AFTER CESSATION OF CARBIMAZOLE	SMOOTH CASES = 21		NODULAR CASES = 12		NOT + CASES = 7		TOTAL
	Rem.	Rel.	Rem.	Rel.	Rem.	Rel.	
0-6	2	2	1	6	1	–	12
7-12	5	1	2	–	1	1	10
13-18	5	–	1	1	–	1	8
19-24	2	2	–	1	1	–	6
25-30	2	–	–	–	2	–	4
0-30	16	5	4	8	5	2	40
% of gland type fully treated -	76	24	33	67	71	29	

Total remissions in 40 selected cases = 25 (62.5%).
Total remissions in 60 unselected cases = 25 (42.0%).
Rem. = Remissions. Rel. = Relapses. Not + = Thyroid not enlarged.

is shown in Table 2. Of the 21 patients with smooth goitres treated on carbimazole, there has been a remission for from 5-30 months in 16 (76 per cent.). The corresponding figure for nodular goitre was 33 per cent. Patients without thyroid enlargement numbered 7. Of these, 5 (71 per cent.) have remained euthyroid on stopping the drug. The rate of remission of the total 60 unselected patients has been 42 per cent.

Of the relapsing cases, 53 per cent. of all failures have occurred in the first 6 months and 67 per cent. within a year. Seventy-five per cent. of the relapses affecting nodular glands were detected within 6 months.

2. Effect on the Eye Signs.

Of the 60 patients, eye signs were observed in 31. They occurred with about equal frequency and severity in the gland types (Fig. 2). A thyrotoxic stare was present in 6, while there was moderate exophthalmos in 21 and severe eye changes in 4. The eyes were normal in the 29 remaining cases. Table 3 shows the effects of treatment on the eye signs. In 36 patients (60 per cent.) the eyes were unchanged, in 19 (31.5 per cent.) there was improvement, and in 5 (8.5 per cent.) the exophthalmos was aggravated. All these last cases constituted relapses or cases unsuited to medical treatment alone.

Of the 4 patients with severe exophthalmos, 2 had ophthalmoplegia. Both showed some improvement in the eye signs on carbimazole. In one of the remaining cases the exophthalmos remained unchanged in spite of clinical remission of the disease process. In the other the eye signs became worse because treatment was carried out irregularly. This patient was elderly, had a small nodular gland, and was treated electively by radioactive iodine.

TABLE 3.

Analysis of Change of Eye Signs in 60 Thyrotoxic Patients on Carbimazole.

Treatment Category on Carbimazole	Eye signs in sixty cases: Unchanged Sm.	Nod.	Not +	Total %	Improved Sm.	Nod.	Not +	Total %	Worse Sm.	Nod.	Not +	Total %
Remissions	12	2	4	18 (72%)	4	2	1	7 (28%)	–	–	–	–
Relapses	2	4	1	7 (47%)	3	3	–	6 (40%)	–	1	1	2 (13%)
Elective Surgery	4	2	–	6 (67%)	2	–	–	2 (22%)	–	1	–	1 (11%)
Elective I_{131}	2	–	–	2 (67%)	–	–	–	–	–	1	–	1 (33%)
Remaining Cases	3	–	–	3 (37.5%)	–	4	–	4 (50%)	1	–	–	1 (12.5%)
Total Cases	23	8	5	36 (60%)	9	9	1	19 (31.5%)	1	3	1	5 (8.5%)

Sm. = Smooth. Nod. = Nodular. Not + = Thyroid not enlarged.

TABLE 4.

Analysis of Change in Gland Size in 60 Thyrotoxic Patients on Carbimazole.

Treatment Category on Carbimazole	Gland size in sixty cases: Unchanged Sm.	Nod.	Not +	Total %	Decreased Sm.	Nod.	Not +	Total %	Increased Sm.	Nod.	Not +	Total %
Remissions	5	2	5	12 (48%)	11	2	–	13 (52%)	–	–	–	–
Relapses	3	6	1	10 (67%)	2	2	–	4 (27%)	–	–	1	1 (6%)
Elective Surgery	1	3	–	4 (44%)	–	–	–	–	5	–	–	5 (56%)
Elective I_{131}	1	1	–	2 (67%)	–	–	–	–	1	–	–	1 (33%)
Remaining Cases	4	2	–	6 (75%)	–	2	–	2 (25%)	–	–	–	–
Total	14	14	6	34 (57%)	13	6	–	19 (32%)	6	–	1	7 (11%)

Sm. = Smooth. Nod. = Nodular. Not + = Thyroid not enlarged.

3. Effect on Gland Size and Consistency at Operation.

The outcome of carbimazole therapy on gland size was noted in all 60 patients (Table 4). The gland was unchanged in 34 (67 per cent.), decreased in size in 19 (32 per cent.) and increased in 7 (11 per cent.) A decrease in gland size was more common in remitting cases—52 per cent. as compared with 27 per cent. in relapses. No case in which the gland increased in size showed a remission.

Surgery was decided on in 5 patients because of the size of the gland on first interview or because of its rapid enlargement in the early stages of carbimazole treatment. All had smooth glands and varied in age from 20-53 years. In 4 others, surgical treatment was considered necessary at the first attendance on account of other factors such as nodularity, age, and mechanical effects. Toxicity was adequately controlled in all 9 patients pre-operatively.

Four patients were treated by sub-total thyroidectomy on account of relapse after adequate duration of treatment. One operation was necessitated by granulopenia complicating carbimazole treatment.

In all, 14 sub-total thyroidectomies were required. Lugol's iodine 5 minims three times daily was given in the 10-14 days before operation concurrently with carbimazole. In all patients the gland was enlarged and vascular. In no instance was it considered friable and no difficulty from bleeding at operation was encountered.

4. Effect on Body Weight.

Weight gain was a constant feature in all cases, though there was great variation in the amount, which varied from 3 lb. to 42 lb. and expressed as a percentage

Fig. 4.

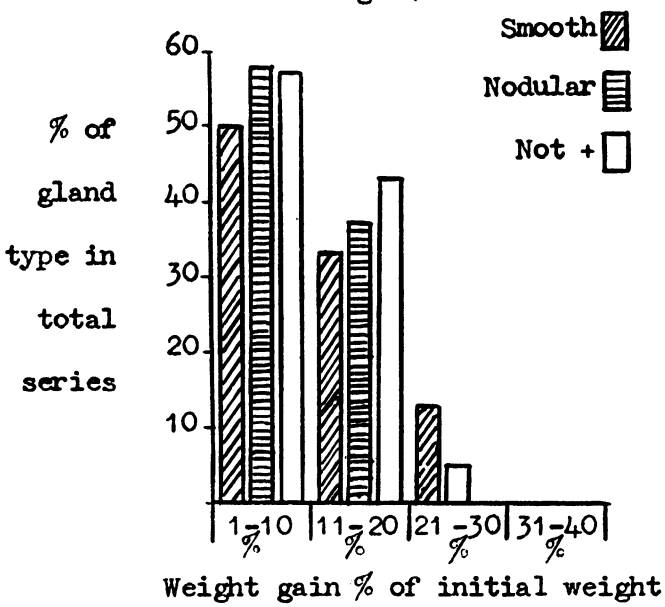

Fig. 4—Percentage weight gain according to gland type.

of the patient's weight on the first attendance was 2 to 33. The average weight gain in cases which remitted was 12.6 lb. (9 per cent.) and in relapsed cases 15.4 lb. (12 per cent.). Fig. 4 shows the weight gain per cent. related to the gland types. This shows no significant difference in the average weight gains in cases with smooth, nodular or "not enlarged" glands. For the cases going to operation the average weight gain was 9 per cent.

Considering the two resistant cases, both with nodular glands, one had a weight gain of only 3.5 per cent. in 36 months while the other gained by 18 per cent. over 29 months.

5. Effect on Associated Pregnancy.

Three patients in the series were pregnant. The first became pregnant during the early stages of carbimazole treatment, and treatment was continued throughout the pregnancy without incident. Four months after completing a 16-months'

TABLE 5.

TOXIC AND ASYMPTOMATIC LEUCOPENIC REACTIONS IN 60 THYROTOXIC PATIENTS ON CARBIMAZOLE.

CASE No.	SEX AND AGE YEARS	AT ONSET: Daily Dosage mgms.	AT ONSET: Stage of Treatment	CLINICAL FEATURES	DIAGNOSIS AND PERCENTAGE INCIDENCE
46	F. 58	45	22 days	Agranulocytic Angina. W.C.C. 3,600 N. 22%	Blood Dyscrasia 1.5%
5	F. 74	45	60 days	Allergic Stomatitis. Contact Dermatitis.	Allergic Reactions 4.5%
28	M. 43	45	10 days	Allergic Erythema.	
35	F. 33	45	14 days	Erythematous rash. W.C.C. 3,200 N. 49%	
1	F. 54	5	12 months	No symptoms. W.C.C. 3,100 N. 42%	Asymptomatic Leucopenia 10.5%
4	F. 53	15	5 months	No symptoms. W.C.C. 1,000 N. 65%	
7	F. 54	45	5 months	No symptoms. W.C.C. 2,800 N. 48%	
9	F. 61	45	3 months	No symptoms. W.C.C. 3,900 N. 47%	
13	F. 38	45	1 month	No symptoms. W.C.C. 3,600 N. 63%	
27	F. 17	45	2 months	No symptoms. W.C.C. 2,700 N. 48%	
30	F. 59	30	5 months	No symptoms. W.C.C. 3,100 N. 58%	

No patient had a history of previous allergy.

Treatment was continued with carbimazole in all except patients Nos. 46 and 35.

course of treatment pregnancy occurred again. She appeared to have undergone remission, no further carbimazole was given and there was no relapse during or immediately following the pregnancy. However, 19 months later she showed slight recurrence of thyrotoxicosis and was treated by sub-total thyroidectomy.

The second patient was pregnant in the last 6 months of carbimazole therapy. Mother and child did satisfactorily and the patient is now euthyroid 15 months following a course of carbimazole lasting 19 months.

The third patient became pregnant 3 months after starting treatment. By the third month of pregnancy control was unsatisfactory, the thyroid enlarged rapidly and she had definite exophthalmos. She was treated by sub-total thyroidectomy and is now euthyroid 17 months later. No eye changes are evident.

6. Toxic Effects.

One patient with agranulocytic angina, 3 with allergic responses, and 7 with asymptomatic leucopenia were observed (Table 5), viz.:—

One female patient of 58 years (Case 46), with a slight smooth goitre, developed a sore throat on the twenty-second day of treatment. The white cell count fell to 3,600 per c.mm. with neutrophil polymorphs 22 per cent. Carbimazole was promptly omitted with subsidence of symptoms. She was successfully treated by radioactive iodine and is now euthyroid some 3 years later.

One patient (Case 5) complained of a sore tongue and mouth after 2 months' treatment with carbimazole. The lesion was allergic in type and readily subsided with local application of neomycin and hydrocortisone solution. There was no associated blood dyscrasia.

After 7 months of treatment the same patient developed a contact dermatitis to carbimazole tablets affecting the left index finger and thumb. This settled spontaneously when she used a spoon for removing the tablets from the jar.

A 43-year-old male patient (Case 28) developed an itchy red rash with "prurigo nodules" ten days after starting treatment. The rash, mainly on the trunk and upper limbs, continued for a month and cleared without interruption of carbimazole therapy. There was a recurrence of the rash six months later. This responded satisfactorily to an anti-histamine drug.

A further patient (Case 35), a 33-year-old woman, also developed a generalised erythematous rash with a leucopenia of 3,200 per c.mm., neutrophil polymorphs 49 per cent. two weeks after starting carbimazole. The drug was withdrawn, and she was satisfactorily treated surgically.

Seven patients were noted on routine white cell counts to have leucopenia. There were no associated symptoms and carbimazole treatment was continued with no ill effects. The figures for white cell counts are shown in Table 5.

Grouping Case 35 as an allergic response, serious blood dyscrasia arose in 1.5 per cent. of cases and simple allergic reaction in 4.5 per cent. Asymptomatic leucopenia was simply a chance routine finding, the blood count returning to a low normal value 1-2 weeks later. The incidence was 10.5 per cent.

TABLE 6.

SUMMARY OF PAIRS OF FACTORS PLOTTED ON SCATTER DIAGRAMS.

NUMBER OF SUBJECTS	x	y
60	Age in years	Duration of symptoms in months
33	Age in years	I_{131} "T" factor
30	Weight gain with treatment as % of initial weight in lbs.	I_{131} "T" factor
50	Weight gain with treatment as % of initial weight in lbs.	Initial weight in lbs.
50	Actual weight gain in lbs. with treatment	Initial weight in lbs.
27	Actual weight gain in lbs. with treatment	Duration till euthyroid in months
50	Weight gain with treatment as % of initial weight	Duration till euthyroid in months
11	Weight gain with treatment	Stage of relapse in months
34	Weight gain with treatment as % of ideal weight	Total carbimazole till euthyroid in gms.
15	Total duration of treatment in months	Stage of relapse in months

No apparent relationship demonstrated.

DISCUSSION.

The potency of a new anti-thyroid substance may be tested by its blocking effect on the uptake of I_{131} by the normal human thyroid (Stanley and Astwood, 1947) or by a similar effect on the thyrotoxic gland (Stanley and Astwood, 1948). Macgregor and Miller (1953), while demonstrating a more potent effect from carbimazole as compared with methimazole in doses as small as 0.5 mgm., using the former technique, stress the caution necessary in transferring the results of potency trials of this type into the clinical field. Doniach (1953) remarked on the fact that such tests do not take into account the cumulative properties of the drug, the individual response to dosage, and the amount of hormone stored in the gland. The same remarks apply to tests of inhibition *in vitro* of the enzymic oxidative iodination of protein (Fraser, *et al.*, 1954). Only by clinical trial can the place of an anti-thyroid substance in treatment and its toxic risk be estimated.

1. Anti-Thyroid Effect.

The decision as to when a euthyroid state has been achieved is a difficult one in most patients. In the present series 6-8 months were necessary for maximum improvement as judged by return to normal of the pulse rate, sweating, tremor, and other signs. In reports from the literature, control is claimed to have been achieved much earlier. McGavack, *et al.* (1956), in 38 patients treated on 30-60 mgm. of carbimazole daily obtained control of thyrotoxic features in 21-84 days (average 35 days), while Kirkeby and Romcke (1955) found toxic symptoms

to cease in 3-12 weeks and Bartel (1953) in an average of 8 weeks. There is no doubting that very considerable improvement was noted in the initial 2 months in all patients treated. No comparable studies of carbimazole combined with thyroxine are available, but in the series of 32 patients treated on methyl thiouracil with thyroxine, Fraser and Wilkinson (1953), a euthyroid response was achieved in 6-8 weeks. Using carbimazole alone, Doniach (1953), in 90 patients with clinical and B.M.R. control, found a return to a euthyroid state in 2-8 weeks in 72 subjects while 18 cases responded slowly, requiring 3-6 months. She considered these slow responses due to such factors as insufficient dosage and associated psychological stress, and noted a high proportion of elderly patients with small nodular glands among the resistant subjects. She further postulated in some instances of resistance that such patients might detoxicate or excrete the drug rapidly and so require a higher dosage.

None of these factors appears to be operative in the present series and the slow development of euthyroidism can be accounted for only by different criteria of assessment for in all cases the patient had to satisfy the most meticulous criteria of normality before being judged euthyroid, special attention being paid to absence of tremor and sweating, coupled with the return of normal energy, a normal resting pulse rate and maximum weight gain.

In regard to the resistant cases in the present study, one was a man of 43 years who required 36 months of treatment before toxicity was controlled, the other a 39-year-old woman who became euthyroid only after 29 months. Both had moderately enlarged nodular glands, and had carbimazole 45 mgm., and at times 60 mgm., with 1 thyroxine 0.1 mgm. twice daily with only partial control. Hernberg and Lamberg (1957) record 4 cases out of 81 in whom not even a primary response occurred on "thyrostatic drugs." The reason for these resistant cases is not clear.

2. Effect on Eye Signs and Gland Size.

Eye signs were not noted so frequently in this series as in that of Doniach (30 in 60 cases as compared with 63 in 90 cases). Only 3 patients had aggravation of eye signs as compared with 5 in the present series. Goitrogenesis in the present study had an incidence of 11 per cent. as compared with 6 per cent. in that of Doniach. Neither the effect on the eye signs nor the goitre appear to particularly commend the routine addition of thyroxine to treatment. It must be noted, however, that Doniach's was a very closely controlled group of patients. In routine out-patient management, the intervals between attendances for adjustment of dosage may be longer and marked aggravation of eye signs and gland size might arise from overdosage. In support of this, Fraser, *et al.* (1954), in 113 patients treated on methimazole and carbimazole with added thyroxine found no aggravation of eye signs nor any instance of goitrogenesis.

3. The Incidence of Remission.

In this series the rate of 62.5 per cent. for remissions of from 5-30 months for all gland types treated definitively with carbimazole compares very well with any results so far reported for other thyrostatic drugs. Hernberg and Lamberg

report a 25 per cent. remission rate following mixed anti-thyroid treatment in 85 patients, 60 of which had nodular glands. Of the smooth gland patients, their remission rate of 73.8 per cent. is very similar to that of the present group (76 per cent.). Other studies on results obtained with long-term treatment with propyl thiouracil are those of McCullagh and Cassidy (1953), who reported a remission rate of 66.7 per cent. in 60 patients with smooth goitre 4 years after stopping the treatment, and of Iversen (1951, 1955), who reported a 79.6 per cent. remission rate in a series of 144 patients treated on methyl thiouracil. Similarly, Aspenstrom (1953), using propyl thiouracil, observed remission in 75 per cent. of subjects with smooth goitre and 65 per cent. of those with nodular glands.

4. Toxic Reactions.

Several papers deal with the low incidence of toxic complications of carbimazole as compared with other thyrostatic drugs. Doniach (1953) reported absence of toxicity in 150 patients. Bartel (1953), in a series of 52 cases, described 2 patients with skin rashes and 1 with agranulocytic angina; an incidence of 6 per cent. total or 2.0 per cent. of serious reaction. The agranulocytic patient had a white cell count of 2,000 per c.mm. with no polymorphonuclear cells. Fraser, *et al.* (1954), in 57 patients on carbimazole had one instance of agranulocytosis in a patient who had previously suffered from skin and joint symptoms with methimazole. The reaction to carbimazole arose 5 weeks after changing to this drug. The white cell count fell to 2,000, polymorphs 3 per cent., and returned to normal in 10 days. Harrison (1954) and Shaw (1955) each recorded a case of agranulocytosis on carbimazole with recovery. Greene and Morgan (1956), in a series of 181 patients, found 4 with harmless rashes in whom treatment could be continued. Two patients developed purpura, 1 pretibial myxœdema, and 1 pure red cell anæmia, all necessitating treatment by sub-total thyroidectomy. This represented an incidence of serious side effects in 0.6 per cent. By summation of the 435 cases reported at that time, they noted the occurrence of rashes in 1.6 per cent., agranulocytosis in 0.7 per cent., and pancytopenia and pure red cell anæmia in 0.1 per cent. each. The total toxic reaction of 3.4 per cent. compares favourably with that for methyl thiouracil quoted by Greene and Morgan (1956) as 5.8 per cent. Burrell, *et al.* (1956), reported on 1,046 cases regarding toxicity. The incidence of major toxic reactions (marrow aplasia, fever, lymphadenopathy and arthralgia) was 0.5 per cent. and minor reactions (rashes, nausea, headache, etc.) in 1.5 per cent. The first fatal case of marrow aplasia arising with carbimazole treatment was described by Richardson, *et al.* (1954). Further fatal cases have been published by Burrell (1956) and Tait (1957).

In the present series, one case of agranulocytic angina was encountered, representing an incidence of 1.5 per cent. In view of the small number of patients studied, this figure is probably an exaggeration of the true risk. The same applies to the development of minor allergic complications, the occurrence of generalised rashes in this series in 4.5 per cent. being rather higher in incidence than elsewhere reported. I have so far not found any previous account of contact dermatitis to the carbimazole tablet such as arose in one case in this series.

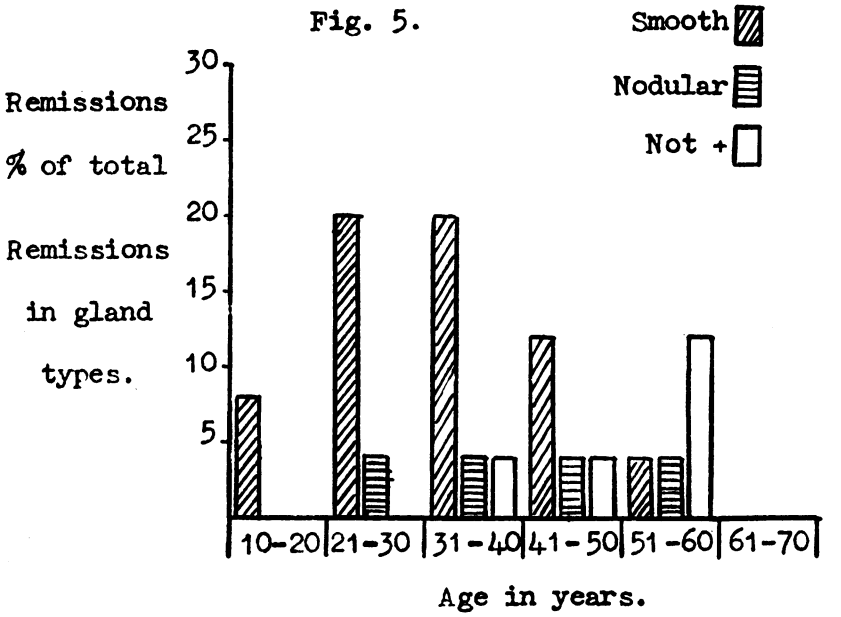

Fig. 5—Remissions in gland types grouped according to age.

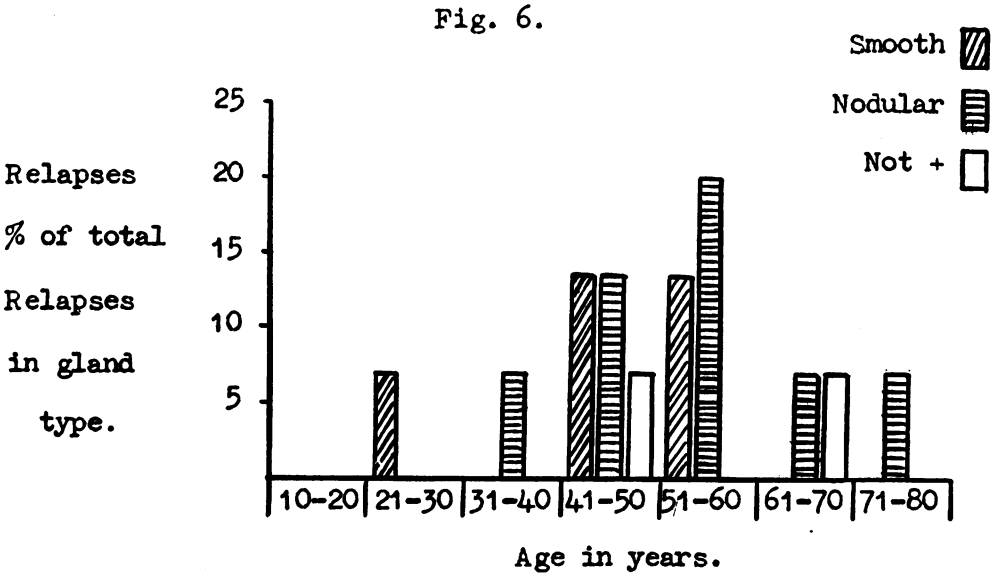

Fig. 6—Relapses in gland types grouped according to age.

5. Factors influencing Response to Treatment.

All investigators agree that carbimazole is an effective anti-thyroid agent with a definite, but slight toxic risk. Except for the rare resistant cases cited above, all patients with thyrotoxic glands will be controlled by the drug whether the eventual treatment is by thyroidectomy, radioactive iodine or the patient be continued on definitive drug treatment.

In the last group of patients, certain factors undoubtedly influence the therapeutic response. Among the most important are age and gland type. Remissions and relapses expressed as a percentage of the gland types in relationship to age groups are shown in Figs. 5 and 6 respectively. Fifty-one per cent. of the remissions up to the age of 40 years involve smooth glands, and the total remissions of all types before the age of 40 constitute 60 per cent. By the age of 50 years, 80 per cent. of remissions have occurred so that the chances of obtaining permanent control on stopping carbimazole beyond this age group are small. Remissions among nodular glands form a small constant fraction of the total remissions from the age of 30 years onwards. The cases in which there was no glandular enlargement are relatively few. They appear, however, to give a peak of incidence in the 50-60 age group and 5 out of the 7 cases have had remissions of 6, 8, 20, 28, and 29 months respectively. The incidence of remission in even this small group of patients is high and the impression is that they behave more like smooth glands in their good response and long remission on carbimazole.

In order to explore further any factors which might possibly relate themselves numerically, scatter diagrams were drawn against the factors shown in Fig. 6. It was clear from these diagrams that there was no obvious relationship. Goodwin, *et al.* (1954), in a statistical analysis of the long-term treatment of thyrotoxicosis with thiouracil compounds were unable to find a significant relationship between age, length of illness, length of treatment before the drug was withdrawn and the length of remission obtained in 94 patients. They concluded that other factors such as intercurrent infection and social maladjustment as suggested by Douglas and Kennie (1952) might be more important in determining a patient's response on withdrawing thiouracil treatment. It seems likely that this is so. The complex endocrine and other ætiological factors and the influence of the psychological aspect and "make up" of the sufferer undoubtedly play their part. It is, therefore, not surprising that no statistical connections can be found.

The present study supports the observation that young patients with primary thyrotoxicosis are most likely to have a satisfactory remission on carbimazole. Diminution of exophthalmos and gland size or absence of aggravation of these features are more common in remitting cases. Weight gain indicates immediate improvement but is of no prognostic importance regarding duration or permanency of remission. It cannot be related quantitatively to the initial weight taken as an index of weight loss, the duration of treatment till euthyroid, nor to the total amount of carbimazole given till symptoms are controlled. Weight gain is further unrelated to the I_{131} T factor, using it as indicative of the severity of the hyperthyroidism. There is no evident relationship between the amount of weight gained and the stage of relapse for any gland type.

Summary.

A series of 60 thyrotoxic patients was studied, of which 40 were treated on carbimazole and thyroxine. Two patients proved resistant. Six to eight months were required to render the patients euthyroid. Remissions of 5-30 months occurred in 62.5 per cent. of cases and 76 per cent. of the smooth glands remitted. The majority of relapses arose within a year.

The effect of treatment on the eye signs, gland size and consistency, body weight and associated pregnancy are recorded. Toxic complications arose in 4 patients, including 1 with agranulocytic angina with recovery. The occurrence of contact dermatitis to the tablet is described.

Factors related to the anti-thyroid effect are discussed. No relationship could be found in regard to age, duration of symptoms, I_{131} T factor, initial weight of patient, percentage or actual weight gain, duration of treatment or total quantity of carbimazole till euthyroid, total length of treatment given and the stage of relapse.

The following facts emerge:—

1. Carbimazole is a potent anti-thyroid drug with a very low toxic risk.
2. Age and gland type are the most important factors in selection of cases for treatment, young subjects with smooth glands giving most remissions.
3. In the few cases available for study, those without clinical thyroid enlargement appear to respond as well as smooth cases in spite of their later age of presentation.
4. Weight gain occurs in all cases and is variable.
5. Remission is unlikely in cases where the eye changes are aggravated or the gland enlarges in spite of added thyroxine.
6. Certain resistant cases occur. They constituted 3 per cent. of the series. The reason for the resistance is obscure.

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References.

Aspenstrom, G. (1953). *Acta Med. Scandinav.*, **147**, 63.

Astwood, E. B., Sullivan, J., Bissell, A., Tyslowitz, R. (1943). *Endocrinology*, **32**, 210.

Bartel, E. C. (1953). *J. Clin. Endocr.*, **13**, 1305.

Burrell, C. D., Fraser, R., Doniach, D. (1956). *Brit. med. J.*, **1**, 1453.

Burrell, C. D. (1956). *Brit. med. J.*, **1**, 1456.

Doniach, D. (1953). *Lancet*, **1**, 873.

Douglas, D., Kennie, A. T. (1952). *Brit. med. J.*, **2**, 1387.

Fraser, R., Wilkinson, M. (1953). *Brit. med. J.*, **1**, 481.

Fraser, T. R., Garrod, O., Hanno, M. G.W., and Jadresic, A. (1954). *J. Clin. Endocr.*, **14**, 1230.

Goodwin, J. E., Steinberg, H., and Wilson, A. (1954). *Brit. med. J.*, **1**, 422.

GREENE, R., MORGAN, D. C. (1956). *J. Clin. Endocr.*, **16**, 391.
HARRISON, A. R. (1954). *Lancet*, **1**, 396.
HERNBERG, C. A., LAMBERG, B. A. (1957). *Acta Endocr., Copenhagen*, **24**, 263.
IVERSEN, K. (1951). *J. Clin. Endocr.*, **11**, 298.
IVERSEN, K. (1955). *Inaugural Speeches at the XXVII Meeting of the Scandinavian Surgical Society*, Oslo, p. 104.
KIRKEBY, K., ROMCKE, O. (1955). *Lancet*, **1**, 374.
LAWSON, A., RIMINGTON, C., SEARLE, C. E. (1951). *Lancet*, **2**, 619.
LAWSON, A., BARRY, G. (1951). *Lancet*, **2**, 621.
McCULLAGH, E. P., CASSIDY, C. E. (1953). *J. Clin. Endocr.*, **13**, 1507.
McGAVACK, T. H., CHEVALLEY, J., RECKENDORF, H. K., and HAAR, H. O. (1956). *J. Clin. Endocr.*, **16**, 887.
MACGREGOR, A. G., MILLER, H. (1953). *Lancet*, **1**, 881.
POATE, SIR H. (1953). *Lancet*, **1**, 879.
PURVES, H. D. (1943). *Brit. J. exp. Path.*, **24**, 171.
RICHARDSON, J. S., SARKANY, I., CAMPBELL, C. D. (1954). *Brit. med. J.*, **1**, 364.
SHAW, A. B. (1955). *Brit. med. J.*, **2**, 246.
STANLEY, M. M., ASTWOOD, E. B. (1947). *Endocrinology*, **41**, 66.
STANLEY, M. M., ASTWOOD, E. B. (1948). *Endocrinology*, **42**, 107.
TAIT, G. B. (1957). *Lancet*, **1**, 303.

REVIEWS

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